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| 08-779-002 | 06-08-97 | JANIS K FRASER | 102-17-0010 |

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| EXAMINER |
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DEPARTMENT OF COMMERCE

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| ART UNIT | PAPER NUMBER |
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4

1819

DATE MAILED: 06/08/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

- Responsive to communication(s) filed on _____
 This action is FINAL.
 Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- Claim(s) 1, 19, 21-26 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
 Claim(s) _____ is/are allowed.
 Claim(s) 1, 19, 21-26 is/are rejected.
 Claim(s) _____ is/are objected to.
 Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
 The drawing(s) filed on _____ is/are objected to by the Examiner.
 The proposed drawing correction, filed on _____ is approved disapproved.
 The specification is objected to by the Examiner.
 The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 All Some* None of the CERTIFIED copies of the priority documents have been

- received.
 received in Application No. (Series Code/Serial Number) _____
 received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- Notice of Reference Cited, PTO-892
 Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
 Interview Summary, PTO-413
 Notice of Draftsperson's Patent Drawing Review, PTO-948
 Notice of Informal Patent Application, PTO-152

— ON THE FOLLOWING PAGES —

Paper # 4
5/8/97

DETAILED ACTION

Preliminary amendments filed on 11/19/96 have been incorporated. Claims 2-18 and 20 are canceled and claims 1, 19 and 21-26 are pending and will be examined in this Office action.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 1 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of copending Application No. 08/311157. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

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A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 26 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26, 31, 32 and 38 of copending Application No. 08/311157. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 26 of the instant application is drawn to a nucleic acid expressed in a baculovirus vector while claims 26, 31, 32 and 38 of copending application are drawn to a nucleic acid or a cell containing a nucleic acid to be expressed in a baculovirus vector. They are obvious variants because they only differ in the to be expressed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

Claims 1, 19, 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing an exogenous gene in vitro in a mammalian cell by introducing a into the cell a baculovirus comprising the said gene, does not reasonably provide enablement expressing the gene in vivo such that the infected cell will be alive and will provide treatment of a gene deficiency disease. The specification does not enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The broad claims are drawn to a method of expressing any gene in any cell in vitro or in vivo using a baculovirus vector for treating any gene deficiency disease. However, the specification is not enabling for practicing such broad claims pertaining to this invention. The specification does not teach how any and all exogenous genes can be expressed in vivo and that the cells will be alive, or how any deficiency disorder can be treated by expressing desired genes. The specification is only enabling for the expression of genes in vitro because in vivo expression relating to gene therapy has not yet been successful.

The specification is talking about treating various gene deficiency diseases using baculovirus mediated exogenous gene expression. The specification does not provide any evidence of expressing a therapeutic gene such that there is amelioration of a disease. The specification has shown some in vitro expression of a marker gene β -galactosidase in HepG2 cells, and very poor expression in 3T3 mouse fibroblasts and in human hepatocytes SKHep1, which clearly suggests that not all cells are capable of expressing exogenous genes at a high level. The specification has shown somewhat better expression in only HepG2 cells because these cells contain asialoglycoprotein receptor, but the specification has not shown expression of a therapeutic gene in vivo using the desired baculovirus vector. One skilled in the art would not accept that in vitro expression would be successfully translated in in vivo systems and would provide a therapeutic benefit. While recombinant DNA technology is available to infect various cell lines with a recombinant baculovirus, it is not routine in the art to screen large numbers of cell

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lines where the expectation of obtaining productive infection of an exogenous gene is unpredictable based on the instant disclosure and taught in the art as being unlikely to be successful. Therefore, one skilled in the art would require guidance, such as the necessary baculovirus modifications or the characteristics of mammalian cells which allow increased expression in order to make and use expression methods in a manner reasonably correlated with the scope of the claims. Without such guidance, the skilled artisan would require undue experimentation to practice the invention.

The specification has not taught what is the level of expression of the desired therapeutic gene in vivo, viability of the infected cells in vivo, and correlation between the expression of the desired gene and the disease treatment. The specification suggests using various therapeutic genes for treating various diseases, but there is no working example showing any specific disease treatment. There are no guidelines, suggestions, or data that support that the system would be effective in an in vivo treatment using cell or gene therapy means. Mere description of a system is not sufficient for an artisan to practice the invention and would require undue experimentation. Gene therapy in general is an unpredictable art and many problems still need to be solved in order to use this method with a success. Major problems are known to be delivery of genes to target cells, expression of the gene, stability of the transduced gene and types of cells expressing the gene. Expression of a therapeutic protein in vivo to a therapeutic level is not generally obtained in the art. In this regard, recent reviews indicate that expression of a desired therapeutic gene is usually low in vivo, depends on the gene, and requires an accurate and efficient delivery system

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(FASEB J. 1995, Vol. 9, p. 190, col.1). Recent reviews also teach that efficient delivery and expression of foreign DNA has not been achieved by any method. For example, Marshall states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (Science, 1995, Vol. 269, p.1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (Science, 1995, Vol. 269, p.1054, col. 3). There is no evidence that the claimed invention overcomes these art recognized problems.

For the reasons discussed above it would require undue experimentation for one skilled in the art to make and use the claimed methods and compositions, particularly given the quantity of experimentation, the amount of direction or guidance presented, the absence of working examples for in vivo gene expression and treatment of a disease associated with a gene of deficiency, the unpredictability of the art and the breadth of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 19 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (US patent 5,004,687) in view of Fraser (Curr Top Microbiol Immunol 158: 131-172, 1992) and

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Srivastava (US patent 5, 252,479, effective filing date Nov. 8, 1991). Miller teaches the use of a baculovirus expression vector (transplacement vector) in the expression of exogenous genes under the Rous Sarcoma Virus (RSV) long terminal repeat (LTR) promoter in insect and mammalian cells (col. 5, line 1 through col. 6, line 37). Miller discloses the expression of marker genes such as the chloramphenicol acetyl transferase (CAT) gene under the RSV LTR in mouse cells (col. 7 line 68 through col. 8 line 15). Miller states that this baculovirus vector system is valuable because this system is expressing exogenous gene products in hosts which are otherwise not susceptible to pathogenic effects of the virus (col. 4, line 34 to line 37). Miller et al does not teach expression of mammalian genes, antisense genes or ribozyme genes. Fraser teaches baculovirus expression vectors for expressing mammalian genes (pp 145- 146). Srivastava teaches expression of antisense genes using an AAV vector for the purpose of gene therapy by preventing the translation of its target mRNA or transcription of its target DNA (col 6 line 61 to col 7 line 48) .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the baculovirus vectors of Miller for expressing mammalian genes as taught by Fraser with the expectation to get increased expression of mammalian genes and without any pathogenic effects to the host cells as taught by Miller. One could also express the antisense genes or ribozyme genes by inserting the gene into baculovirus vector since this is a non-pathogenic virus. The motivation to use baculovirus vector for expressing mammalian genes is provided by Fraser

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who teaches that baculovirus can be used for efficient expression of large and potentially cytotoxic mammalian gene products (p. 145, para 2) and by Miller who teaches that the virus is non-pathogenic. There would be a reasonable expectation of success given the data of miller and Fraser. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (US patent 5,004,687) in view of Fraser (Curr Top Microbiol Immunol 158: 131-172, 1992), Grompe et al (Adv. In Experimental Medicine and Biology 3098:51-56, 1991) and Wilson et al (J. Biol. Chem 267: 963-967, 1992). Miller and Fraser teach use of baculovirus vectors for expressing mammalian genes in mammalian cells as described above. They do not teach gene therapy of a deficiency disorder in hepatocytes. Grompe et al teach gene therapy in man and mice in deficiency disorders of adenosine deaminase (ADA), ornithine transcarbamylase (OTC) and muscular dystrophin gene (see abstract). Grompe et al teach gene therapy of ADA-deficient patient using human ADA complementary DNA (cDNA) in a retroviral vector (p. 52, para 1). Grompe et al also teach gene therapy targeted at the liver expressing the human in mice models (p. 54, para 1). Wilson et al teach hepatocyte-directed gene transfer *in vivo* resulting in transient improvement of hypercholesterolemia in low density lipoprotein receptor-deficient rabbits (see abstract). Wilson et al teach a method gene transfer for gene therapy using an asialoglycoprotein-polycation conjugate consisting of asialoorosomucoid (ASOR) coupled to poly-L-lysine and

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soluble DNA vector that is capable of targeting to specifically hepatocytes via asialoglycoprotein receptors present on these cells (p. 963, col. 2 para 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the baculovirus vectors of Miller for expressing mammalian genes as taught by Fraser with the expectation to get increased expression of mammalian genes and without any pathogenic effects to the host cells as taught by Miller. One would be expected to use baculovirus vector for gene therapy using the desired gene such as the LDL receptor gene since the vector can be expressed in mammalian cells and nonpathogenic to hosts as taught by Miller et al. Both Miller and Fraser provide motivation to use baculovirus vector for expression of mammalian genes as Fraser teaches that baculovirus can be used for efficient expression of large and potentially cytotoxic mammalian gene products (p. 145, para 2) and Miller teaches that the virus is non-pathogenic. One could study the method of Wilson et al for baculovirus vector for liver-specific gene transfer in mammals since it can be expressed in mammalian cells. There would be a reasonable expectation of success given the data of Miller, Fraser, Wilson et al and Grompe et al.. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdur Razzaque whose telephone number is (703) 305-4061. The examiner can normally be reached on from 8:30 to 5:00 (Eastern time).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Abdur Razzaque

May 7, 1997


BRUCE R. CAMPBELL
PRIMARY EXAMINER
GROUP 1800

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The amendment and declaration of Frederick M. Boyce filed October 8, 1997 have been entered.

The specification does not comply with the rules for nucleotide sequence disclosures, 37 CFR 1.821-1.825. The specification contains nucleotide sequences that are not identified by SEQ ID No. at p. 7, lines 19-20. Sequences must be identified by SEQ ID No. each time they are mentioned in the disclosure. See 37 CFR 1.821(d). Correction may require submission of a new sequence listing. If so, Applicants must submit a substitute sequence listing in both computer readable and paper forms, a statement that the two forms are identical, and an amendment directing the entry of the paper form into the specification. The specification should also be amended to identify the sequences pointed out above by SEQ ID No. See the attached "Notice to Comply."

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 26 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 26 of copending Application No. 08/311,157. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The provisional obviousness-type double patenting rejection of claim 1 is withdrawn in view of the amendment to the claim. Since *in vitro* methods were elected in both 08/311,157 and allowed application 08/486,341, the *in vivo* method claimed in the instant application is distinct.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 21-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, as previously stated (paper 4, pp. 3-6).

Applicant argues that the specification is enabling, citing the Boyce declaration. This argument is not persuasive. While the declaration demonstrates that baculovirus can be used to transiently express exogenous genes in a variety of cell types by *in vivo* administration, it does not show that one skilled in the art would be able to obtain a significant therapeutic benefit from such expression without undue experimentation. As stated in the previous Office action, sustained, high-level expression of introduced genes (required for gene therapy) is not routinely obtainable by those skilled in the art. Applicant's own publication (Boyce et al., ref. ES) shows that gene expression "peaks 12-24 hr postinfection and declines thereafter" (Fig. 4 and paragraph bridging pp. 2350-2351). It is no coincidence that the experiments described in the declaration measured gene expression after 24 hours. Boyce et al. conclude, "Much more work will be necessary to evaluate the...efficacy of AcMNPV as a tool for human gene therapy" (p. 2352, col. 2). Since this was published 18 months after the effective filing date of the instant application, any argument that the specification was enabling at the time the invention was made is not persuasive.

Claim 1 is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory

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action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce Campell, whose telephone number is 703-308-4205. The examiner can normally be reached on Monday-Thursday from 8:00 to 4:30 (Eastern time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1800 are 703-305-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Bruce Campell



BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800